REMARKS

It is desired to thank the Office for its most helpful and careful review of this application and several of mostly counsel's errors, unfortunately occasioned by difficulty in coordinating the study and analysis of the Office criticisms and grounds of rejection by applicant Dr. Jan Vijg during his hectic world-wide travels, and by his associates Dr. Jan Orsouw (in Holland) and Mr. David Rines who assisted in the development of the present invention at the Harvard Medical Research Laboratory at the Beth Israel-Deaconess Hospital complex in Cambridge, Massachusetts.

All have now coordinated and have made a very serious effort to address each of the Office criticisms and requirements to place this application finally in condition for allowance.

Turning, first, to *paragraph* 2 of the outstanding Office action, the appropriate claims 5 and 6 have been replaced from the October 25, 2000 amendment as suggested by the Examiner, with the proper status and subject matter identification provided in the set of claims currently presented herein.

The uniformity objection of *paragraph 3* of the Office action has been remedied by adding the required period in claim 11.

The objection in *paragraph 4* to claims 4-6 and 10, 11, 13 and 14 (claims 12 and 15-17 being herein withdrawn), as referencing tables instead of SEQ ID NOS. has also been remedied.

The requirement of *paragraph 5* to cancel Table 4 as adding "new matter" is complied with herein.

The Examiner is indeed correct that while

> "the originally filed specification listed a clamp name next to a specific primer sequence (see p. 10 of specification as originally filed)... neither a SEQ ID NO. nor an actual sequence were taught corresponding to the clamp name."

It is further correctly stated by the Examiner that

> "the clamp names... (GC3, GC13, GC12, etc.) do not correspond to the names given the actual GC clamps set forth in the specification as originally filed."

Applicant will later address the linking of the computer output file herein to the clamp sequences that were, however, actually disclosed in the original specification.

Turning to *paragraphs 6 and 7,* the Office has rejected claim 12 under 35 U.S.C. 112, first paragraph, as involving "new matter" in setting forth "a method that excludes short range PCR" contrary to the teaching of the specification. This was not applicant's intention in presenting this claim, and therefore claim 12 has been withdrawn.

In *paragraphs 8 and 9,* claims 10-14 (claim 12 now having been canceled, as above) have been rejected under 35 U.S.C. 112, second paragraph, as indefinite and unclear as to whether "the primer pairs listed are responsible for only the exon fragments listed", and for exon 20 being listed twice.

Claims 10, 11, 13 and 14 have accordingly been amended to provide clarification and in a manner that also addresses the earlier-discussed lack of correspondence of the clamp names (GC 3, GC 13, GC 12, etc. on pages 10-12 of the specification) "to the names given the actual GC clamps set forth in the specification as originally filed."

The original specification, however, in footnote "[1]GC clamps" on immediately earlier pages 7 and 8 of the original specification, provided the specific clamp sequences "50, 45, 40, 8, 5, and 2" clamps. The linking of the computer output file to these clamp sequences disclosed in the original specification, is as follows:

Computer File Designation	GC clamp from original specification	SEQ ID NO that applies
GC [1]	40 clamp	SEQ ID NO: 29
GC [3]	40 clamp	SEQ ID NO: 29
GC [4]	50 clamp	SEQ ID NO: 27
GC [8]	50 clamp	SEQ ID NO: 27
GC [18]	45 clamp	SEQ ID NO: 28
GC [11]	2 clamp	SEQ ID NO: 32
GC [12]	5 clamp	SEQ ID NO: 31
GC [13]	8 clamp	SEQ ID NO: 30
GC [16]	8 clamp	SEQ ID NO: 30

Claim 10 has thus been amended clearly to recite these SEQ ID NOS, in first reciting:

"long distance multiplex PCR, using primer pair sequences SEQ ID NOS: 35 and 36, 37 and 38, 39 and 40, 41 and 42, 43 and 44, 45 and 46 to produce a first set of 7 PCR amplification products including exons 1 through 3, 5 through 9, 10 and 11, 12 and 13, 14 through 17, 18 through 20, and 21 through 24, respectively;"

and then reciting:

"subjecting this first set of PCR amplification products to short distance multiplex PCR using primer pairs SEQ ID NOS: 47 and 48 through 119 and 120 to produce 37 short PCR products including/encompassing exons 2 through 24 of the BRCA1 gene; "

and with the GC clamping sequencing step then set forth as:

"(c) using GC clamp sequences SEQ ID NOS: 27, 28, 29, 30, 31 and 32 attached to one or both sequences of each short multiplex PCR primer pair; and"

concluding with:

"(d) subjecting the short PCR products to two-dimensional gel electrophoresis to produce a characteristic spot pattern for specific mutations in the BRCA 1 gene."

Claim 11 depends from amended claim 10 and therefore is now also believed to be definite and clear.

Similarly for dependent claims 13 and 14 which now specify the GC clamp SEQ ID NOS: within the contemplation of the original disclosure.

Withdrawal of the 35 U.S.C. 112 second paragraph rejection therefore appears to be in order and is accordingly respectfully requested.

In *paragraphs 10 and 11,* the Office has rejected claims 10-11 and 13-14 under 35 U.S.C. 103 (a) upon reference to applicant's own prior teachings referred to as "Vijg" or "Vijg II", in view of the Shattuck-Eidens recognition of BRCA1 mutations linked to cancer -- the rationale being

> "the ordinary artisan would have had a reasonable expectation of success that using the method taught by Vijg, or Vijg II, primers could be generated that would both successfully amplify the necessary coding

> regions of the BRCA1 gene and provide characteristic 2-D spot pattern for certain mutations as Vijg and Vijg II both teach in extensive detail..."

More specifically, the Office has held that

> "the ordinary artisan would have been motivated to apply the improved method of identifying mutations of Vijg, or the computer aided method of Vijg II, to detect BRCA1 mutations as taught by Shattuck-Eidens";

and the Office has stated that such

> "would be considered *equivalent* in a method of two-dimensional gel electrophoresis, as taught by Vijg or Vijg II in view of Shattuck-Eidens, to the sequences of the instantly claimed invention, *absent secondary considerations.*"

The Office, however, has appreciated that

> "A showing, in declaration format (see MPEP 716.02 (g)), that the primers of the instantly claimed invention were further manipulated in ways not taught by Vijg or Vijg II, would overcome the rejection."

Applicant has now provided such a "showing" in his accompanying Declaration and also in that of David Rines, his research associate. Particularly in paragraphs 3-8 of the latter declaration, the non-obvious features of change in the Vijg pattern procedures that were required by the unique and inordinate 3200b size of the BRCA1 exon 11 (unprecedently occupying 60% of the coding sequence), are detailed.

Finally, in *paragraph 12*, kit claims 4-6 have also been rejected under 35 U.S.C. 103 (a) upon the same combination of references; and further in view of Ahern's teaching of "premade reagents and kits" -- the holding being that the kits of claims 4-6 would thus be "prima facie obvious to one of ordinary skill in the art at the time the invention was made".

While for the reasons above presented, applicant does not agree with any such "obviousness", the Office has further held that, since the applicant is also a common inventor in the cited Vijg and Vijg II references,

> "This rejection under 35 U.S.C. 103 (a) might be overcome by:
> (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention 'by another'".

The accompanying Declaration of the applicant contains such a showing (paragraph 5), thereby obviating this rejection.

Further, it should be noted that both these kit claims and the method claims in their present amended forms, now do list specific combinations of primers or GC clamps (page 20 of Office action).

It would accordingly appear that this application is now in condition for allowance, and such action is therefore respectfully requested.

The kind assistance of the Examiner in the several suggestions, all adopted by applicant, is deeply appreciated.

Any cost occasioned by this filing, including required extensions of time, petition for which is hereby made, and including for petition to revive unintentional abandonment, may be charged to account number 18-1425 of the undersigned attorneys.

Respectfully submitted,

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